

# Generalized periodic discharges

## More light shed on the old “GPEDs”

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Continuous EEG monitoring (cEEG) is increasingly employed to detect nonconvulsive seizures (NCSz) and nonconvulsive status epilepticus (NCSE) in critically ill patients. A recent international survey of 338 neurologists found that 83% use cEEG at least monthly.<sup>1</sup> The growth in cEEG utilization has led to an increase in the recognition of EEG patterns of uncertain diagnostic and prognostic implications. Generalized periodic discharges (GPDs), formerly referred to as generalized periodic epileptiform discharges (GPEDs), represent one such pattern.

GPDs are defined as the repetition of frontal- or occipital-dominant, synchronous, relatively symmetric discharges.<sup>2</sup> They have relatively uniform morphology and duration with a definable and quantifiable interval between consecutive waveforms, with recurrence of the waveform at nearly regular intervals.<sup>2</sup> GPDs were first described with subacute sclerosing panencephalitis in the 1950s; however, they have subsequently been associated with anoxia, Creutzfeldt-Jakob disease, drugs/toxins (including baclofen, lithium, phencyclidine, ketamine, barbiturates, and anesthetics), metabolic encephalopathy, NCSE, and resolution of status epilepticus.<sup>3–7</sup> Despite the recognition of this EEG pattern for decades, its clinical significance is still poorly understood. Some suggest GPDs lie on the ictal-interictal continuum, while others suggest they are simply a marker of underlying brain dysfunction or injury.

In this issue of *Neurology*®, Foreman et al.<sup>8</sup> report on the relevance of GPDs in 200 critically ill adults undergoing cEEG at their institution. Not only is this the largest case series, but it is the first nested case-control study examining the associations of GPDs, seizures, and outcomes. Consecutive patients with GPDs were identified retrospectively from their EEG database and matched for age, etiology, and level of consciousness to 200 patients without GPDs. Overall, 4.5% of more than 3,000 consecutive patients undergoing cEEG had GPDs. Presenting illnesses included acute brain injury (44%), acute

systemic illness (38%), cardiac arrest (15%), and epilepsy (3%).

Perhaps the most important and concerning study finding was the dramatic association between GPDs and NCSz/NCSE. The authors found that a staggering 27% of patients with GPDs had NCSz compared to 8% of controls. Similarly, 22% of patients with GPDs had NCSE compared to 7% of controls, consistent with prior pediatric and adult uncontrolled studies.<sup>3,5</sup> However, GPDs were not associated with convulsive seizures or convulsive status epilepticus. The incidence of seizures was not demonstrably higher in those with GPDs compared to those without (46% vs 34%, a nonsignificant difference). Cardiac arrest, coma, NCSE, and sepsis, but not GPDs, were associated with poor outcome in multivariate analysis. This contrasts to a previous uncontrolled study that associated GPDs with poor outcome, particularly in those with sepsis, a factor associated with mortality in the current study.<sup>9</sup>

Despite the many strengths of this study, the authors acknowledge several limitations, including the usual culprits associated with retrospective studies, heterogeneous patient care and the influence of anti-epileptic drugs (AEDs) or anesthetic agents on their findings.<sup>8</sup> An important limitation was the reliance on their EEG database to identify the EEG patterns of interest, without confirming the accuracy of reporting. While all cEEGs were interpreted by board-certified electroencephalographers, more complex EEG patterns such as GPDs and “triphasic waves” are prone to low interobserver reliability. Foreman and colleagues recognized this limitation, and proposed that standardization of EEG terminology may resolve this issue in future studies.<sup>2</sup> Although “triphasic waves” are classified as GPDs in the ACNS standardized EEG terminology, the distinction between seizure-related GPDs and metabolic-encephalopathy GPDs (“triphasic waves”) continues to be challenging.<sup>3,8</sup> The distinction may be important, though, as patients with metabolic-encephalopathy GPDs

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likely have a lower risk of developing seizures based on their underlying pathology. If Foreman and colleagues had been able to make the distinction between seizure-related GPDs and metabolic-encephalopathy GPDs based on history or EEG characteristics, it is possible the percentage of patients having recorded seizures would have increased. This likely explains why the percentage of patients with seizures following detection of GPDs was 46% in the present study but as high as 89% in others.<sup>10</sup>

Foreman and colleagues are to be applauded for designing this important case-control study aimed at unraveling the mystery of GPDs. In this age of rapidly increasing utilization of cEEG, physicians urgently need guidance as to which EEG patterns warrant aggressive treatment and which do not. In the international survey of neurologists discussed above, AEDs were administered by 63% of neurologists if periodic epileptiform discharges were present and occurring at a frequency faster than 1.5 Hz, but not evolving into definite seizures.<sup>1</sup> Substantial variability in practice related to the management of NCSz and NCSE was identified. The study by Foreman et al., although retrospective in design, substantially adds to a growing body of evidence suggesting that periodic discharges are associated with NCSz and NCSE, and that NCSE is associated with poor outcome. Without cEEG, NCSE would have been missed in the majority of patients, precluding its treatment.

What are the key take-home messages? First, patients identified as having GPDs on routine EEGs should undergo cEEG to identify potential impending NCSE. Second, unequivocal NCSE should be promptly treated when diagnosed. Third, implementation of standardized cEEG terminology should be considered in all centers where cEEG is offered, but with assessment of inter-rater reliability. Among future challenges ahead is the need to determine the role for AEDs in patients with GPDs who have not yet developed seizures and whether there are subgroups of patients in whom GPDs provide independent prognostic information. With the dramatic rise in cEEG utilization internationally, investigators are well positioned to carry out large multicenter studies that will help us solve the final remaining cEEG mys-

teries. This will help us develop recommendations, including clinical decision tools, which are more applicable at the individual patient level.

## DISCLOSURE

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